CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Dimethomorph

Chemical Code # 4003, Tolerance # 52068
SB 950 # New A.I.

6/01/01

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Study not required at this time

Toxicology one-liners are attached.

All record numbers through 145450 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T010601
Thomas Moore, 6/1/01

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

Study not submitted.

CHRONIC TOXICITY, RAT

** 013; 145417; "104 Week Dietary Toxicity Study in Rats" (D.J. Everett, et. al., Inveresk Research International, Tranent, Scotland, Lab. Report # IRI 435140 5778, 9/27/88). SAG 151 (CME 151, Bath DW 11/86, 96.6% a.i.) administered orally in the diet to 20 Sprague-Dawley rats/sex/dose at 0, 200, 750, and 2000 ppm for 104 weeks. Calculated mean concentrations for males: 0, 11.04, 42.75 and 116.14 mg/kg/day, respectively; females: 0, 13.85, 61.13, and 164.26 mg/kg/day, respectively. No treatment-related effects on clinical signs, survival rates, hematology, clinical chemistry and urinalysis were detected. Reduced body weight gain was reported in high dose males (weeks 65-104, 83% of control, $p < 0.01$) and females (weeks 1-40 and 45-96, 83% of control, $p < 0.05$). In addition, mid dose females exhibited reduced body weight gain during the first 88 weeks. Increased incidences of dilated mesenteric blood vessels, arteritis and testicular interstitial cell proliferation (7/20 vs. 2/20, $p < 0.05$) were noted in high dose males during histopathological exam. Increased liver pigmentation and hypertrophy were detected in high dose females. **No adverse effects.** NOEL (M/F) = 200 ppm (based on reduced body weight gain). **acceptable.** (Leung, 6/17/96).

CHRONIC TOXICITY, DOG

** 012; 145414; "SAG 151: 52 Week Dietary Toxicity Study in Dogs" (R. Goburdhun and R.J. Greenough, Inveresk Research International, Musselburgh, Scotland, IRI Project # 636876, 11/11/88). SAG 151 (Batch # DW 11/86, 96.6% purity) administered orally in the diet to 4 beagle dogs/sex/dose at 0, 150, 450, and 1350 for 52 weeks (M: 0, 4.9, 14.7, and 44.6 mg/kg/day, respectively; F: 0, 5.0, 15.7, and 47.0 mg/kg/day, respectively). Convulsive seizures lasting for 30-60 seconds were noted for one high dose male in Weeks 44 and 47. This animal also exhibited signs of salivation, ataxia and subdued behavior. Elevated alkaline phosphatase from week 13 to termination with increased liver weight (M: 433.82 g vs. 368.14 g, $p < 0.05$, F: 412.26 vs. 280.25, $p < 0.01$) was reported in high dose animals. NOAEL (M/F) = 1350 ppm **[No adverse effects].** NOEL (M/F) = 450 ppm (M: 14.7 mg/kg/day, F: 15.7 mg/kg/day, based on elevated alkaline phosphatase and increased liver weight). **acceptable**. (Leung, 7/3/96).

ONCOGENICITY, RAT

**** 015; 145425;** "104 Week Carcinogenicity Study in Rats" (D. J. Everett, et. al., Inveresk Research International, Tranent, Scotland, Lab. Report # 435140, 9/27/88). SAG 151 (Batch DW 11/86, 96.6% a.i.) administered orally in the diet to 50 Sprague Dawley rats/sex/dose at 0, 200, 750, and 2000 ppm for 104 weeks. Calculated mean concentrations for males: 0, 10.50, 39.72 and 110.02 mg/kg/day, respectively; females: 0, 13.02, 52.45, and 144.82 mg/kg/day, respectively. Reduction in body weight gain was detected in mid and high dose females (77% and 62% of control, respectively, $p < 0.05$) and high dose males (86% of control, $p<0.05$) without any significant changes in food consumption. Gross necropsy revealed the presence of cysts in the lumbar lymph nodes (9/50 vs. 2/50, $p<0.05$) and dilated mesenteric blood vessels (13/50 vs. 1/50, $p<0.05$) in high dose males, whereas swollen hindfeet (15/50 vs. 4/50, $p<0.05$) were noted in high dose females. Histopathological exam showed ground glass foci in livers from high dose animals (M: 27/50 vs. 17/50, $p<0.05$; F: 18/50 vs. 12/50, $p<0.05$). **Possible adverse effect:** Equivocal effect on the incidence of testicular interstitial cell adenoma in 2000 ppm males (10/50 vs/ 5/50, $P>0.05$, historical control range from 4 - 20%, mean 10.4%$\pm$ 6.6%). NOEL (M) = 750 ppm (39.72 mg/kg/day), F= 200 ppm (13.02 mg/kg/day), based on reduced weight gain; NOAEL(M) = 750 ppm, (F) = 2000 ppm (based on testicular interstitial cell adenoma); **acceptable.** (Leung, 6/27/96).

ONCOGENICITY, MOUSE

** 016; 145429; "104 Week Dietary Carcinogenicity Study in Mice" (A. Smith, et. al., Inveresk

Research International, Tranent, Scotland, Lab. Project # 435088, 9/13/88). SAG 151 (Batch # DW 11/86, 96.6% purity) administered orally in the diet to 50 CD-1 mice/sex/dose at 0, 10, 100, and 1000 mg/kg/day for 104 weeks. No treatment-related clinical signs or survival rates were detected. High dose males showed a decrease in body weight gain from weeks 17 to 92 (83% of control, $P<0.05$). Gross necropsy and histopathology did not reveal any evidence of treatment-related lesions. No signs of carcinogenicity were detected in either sex at dose levels up to 1000 mg/kg/day. NOAEL (M/F) = 1000 mg/kg/day [**No adverse effects].** NOEL (M) = 100 mg/kg/day (reduced body weight gain), (F) = 1000 mg/day/day (no effects at HDT). **Acceptable** (Leung, 6/27/96).

REPRODUCTION, RAT

** 019; 145435; "Two Generation Oral (Dietary Administration) Reproduction Toxicity Study in Rat (Two Litters in the F1 Generation)" (I. Osterburg, Hazleton Lab. Deutschland GmbH, Muenster, Germany, Lab. Report # 763-460-022, 10/3/90). SAG 151 (Batch # DW 11/86, 96.6% purity) was administered in the diet to 30 Sprague-Dawley rats/dose at 0, 100, 300 and 1000 ppm for 2 generations. Calculated mean daily test article intake for males: 0, 6.3, 18.9, and 63.0 mg/kg/day, respectively; for females: 0, 7.9, 24.0, and 72.6 mg/kg/day, respectively. Report does not identify by animal # the mating pairs. One control and one 300 ppm female from the P generation died on day 1 postpartum. Necropsy revealed dead offspring. High dose females from the P1 generation exhibited lower mean body weight than control during the premating period (weeks 2, 4 - 15, 93.2% of control, $p<0.05$) with reduced food consumption (weeks 1 - 5, 91.9% of control, $p < 0.05$). However, body weight and food consumption were comparable in F1 generation females in all dose groups. **No adverse effects** [Parental NOAEL = Reproductive NOAEL = 1000 ppm]. No treatment-related effects on fertility, reproductive performance, necropsy, and histopathology were detected in animals from the P1 and F1 generation. Nominal Paternal NOEL = 1000 ppm (63 mg/kg), Nominal Maternal NOEL = 300 ppm (24.0 mg/kg, reduced body weight and food consumption), Nominal Reproductive NOEL = 1000 ppm (M: 63 mg/kg, F: 72.6 mg/kg, no effect on fertility and general reproductive performance). **acceptable**. (Leung, 7/12/96).

TERATOLOGY, RAT

** 017; 145430-1; "Oral (Gavage) Teratogenicity Study in the Rat" (W. Mueller, Hazleton Lab. Deutschland GmbH, Munster, Germany, Lab. Project ID. # 460/23, 8/11/89). SAG 151 (Batch DW 11/86, 96.6% purity) suspended in water, was administered by oral gavage to 30 pregnant rats/dose at 0, 20, 60, 160 mg/kg/day on days 6 - 15 of gestation. Due to low number of pregnant rats in the original dose groups, 5 additional pregnant rats were added to the original 25 rats in each group to assure a sufficient number of animals for evaluation. One high dose dam died on day 13 of gestation due to intubation error. One dam at 60 mg/kg and two dams at 160 mg/kg revealed 100% intra-uterine deaths at necropsy. Reduced mean body weight gain from days 6 - 10 of gestation and decreased food consumption from days 6 - 15 were evident. **No adverse effects.** Slight increased mean postimplantation loss (2.2 vs. 0.5, $p > 0.05$) based on slight increased mean number of early resorptions due to two animals with 100% intra-uterine deaths, did not reveal any teratogenic effect. Maternal NOEL = 60 mg/kg/day (reduced mean body weight gain), Developmental NOEL = 60 mg/kg/day (postimplantation loss); **acceptable** (Leung, 7/5/96).

TERATOLOGY, RABBIT

** 018; 145432-4; "Oral (Gavage) Teratogenicity Study in the Rabbit" (W. Muller, Hazleton Lab. Deutschland GmbH, Munster, Germany, Lab. Project ID # 460/24, 6/19/89). CME 151 (Batch # DW 11/86, 96.6% purity) suspended in water, was administered by oral gavage on days 6 - 18 of gestation to 22 inseminated rabbits at 0, 135, 300, and 650 mg/kg/day. Mortalities due to gavage error were reported in all dose groups: 1, 1, 1, and 3, respectively. Other unscheduled deaths included one each in the mid and high dose groups were noted. To assure sufficient number of animals for evaluation 4 inseminated rabbits were added to the original 18 rabbits of each dose group. Three pregnant rabbits at the high dose aborted their fetuses. Reduced mean maternal body weight with food consumption was observed at 650 mg/kg. No evidence of teratogenicity was detected. **No adverse effects.** Maternal NOEL = 300 mg/kg (reduced mean body weight with food consumption), Developmental NOEL = 300 mg/kg (dead fetuses). **acceptable.** (Leung, 7/8/96)

GENE MUTATION

** 52068-020 145436 842 "Bacterial Mutagenicity Test on ZTH 236Z40" by F. Oesch, Institute of Toxicology, University of Mainz, Mainz, Germany (project #SP 783; 11/28/85). Salmonella typhimurium his- strains TA 100, TA 1535, TA 1537 & TA 98 and Escherichia coli trp- strain WP2 uvrA were exposed to ZTH 236Z40 (batch #X84; 97.8% purity) in 2 separate expts. using duplicate or triplicate dishes. Doses in the presence of S9 were 0, 5, 15.8 (only TA 1537, expt. 1), 50, 158 (only TA 1537, expt. 1), 500*, 1580* & 5000* ug/plate (asterisks indicate the presence of a precipitate), and, in the absence of S9, 15.8 (only TA 1537, expt. 1), 50, 158, 500*, 1580* & 5000* ug/plate. Despite the success of several positive control agents (+S9: 10 mg/plate benzo[a]pyrene, 10 or 50 ug/plate 2-aminoanthracene & 90 ug/plate 3-methylcholanthrene; -S9: 1 ug/plate benzo[a]pyrene 4,5-oxide, 10 ug/plate MNNG & 15 ug/plate ENNG), the number of revertant colonies did not increase at any test article concentration, -/+ S9 microsomes. Toxicity, measured by survival of a known number of exogenously added his+ TA 1537 spontaneous revertants in the presence of his- bacteria (usually TA 1537), was not observed. ZTH 236Z40 is not mutagenic in the Ames assay under the conditions tested. **Acceptable.** (Rubin, 6/4/96)

** 52068-020 145437 842 "Detection of Gene Mutations in Somatic Mammalian Cells in Culture: HGPRT-Test with V79 Cells [CME 151-Z50]" by H.G. Miltenburger, Laboratory for Mutagenicity Testing, Technische Hochschule Darmstadt, Germany (project #LMP 180 B; 5/11/87. After plating $8x10^5$ cells/175 cm^2 flask on day 1, cultures were exposed for 4 hr to a range of CME 151-Z50 (batch #Dw 11/86; technical product) concentrations on day 2, subcultured on day 5, subcultured on day 9 at ~6x105 cells/80 cm^2 flask (5 replicates) in the presence of the selective agent (11 mg/ml thioguanine) and fixed/stained for colony counts on day 16. 6 separate experiments -/+ S9 microsomes were conducted at a concentration range between 0 & 230 ug/ml (-S9) and between 0 & 300 ug/ml (+S9). Preliminary experiments generally showed severe toxicity (inhibition of plating efficiency of ~50% or greater) at ~200 mg/ml. Despite the success of the positive controls (-S9, 1 mg/ml ethyl methane sulfonate; +S9, 15.4 ug/ml dimethylbenzanthracene) in increasing the # of mutant colonies per 10^6 cells (i.e., the number of cells capable of forming colonies in the presence of the selective agent), no such behavior is seen at any concentration of test article regardless of the presence or absence of S9 microsomes. The test article is, therefore, not considered mutagenic under the conditions tested. **Acceptable.** (Rubin, 6/6/96)

** 52068-020 145438 842 "Bacterial Mutagenicity Studies with CME-151" by T.M. Brooks & D.E. Wiggins, Sittingbourne Research Centre, Kent, England (project #SBGR.88.241; 1/9/89). Salmonella typhimurium his- strains TA 98, TA 100, TA 1535, TA 1537 & TA 1538, and Escherichia coli trp- strain WP2 uvrA pKM101 were exposed to CME 151 (batch #T3/85; 94% purity) in 2 separate expts. using triplicate dishes. Doses - & + S9 microsomes, were 31.3, 62.5, 125, 250, 500, 1000, 2000 & 5000 ug/plate. Test article precipitation occurred at 1000 ug/plate. Despite the success of several positive control agents, the number of revertant colonies did not increase at any test article concentration, -/+ S9 microsomes. Toxicity, evident in the degradation of the background bacterial lawn, occurred only in the TA 1537 strain (concentration range not reported). CME-151 is not mutagenic in the Ames assay under the conditions tested. **Acceptable.** (Rubin, 6/7/96)

** 52068-020 145440 842 "Evaluation of the Mutagenic Activity of Dimethomorph in an In Vitro Mammalian Cell Gene Mutation Test with V79 Chinese Hamster Cells (with independent repeat)" by E.J. van de Waart, RCC NOTOX B.V., Hambakenwetering, The Netherlands (project #058747; 8/7/91). $6x10^6$ suspended cells (10^6 cells/ml)/dose were exposed for 2 hr to (-S9) 0, 10, 33*, 100*, 133*, 180* & 237 ug/ml Dimethomorph (batch #KSLA/2; 98.6% purity) and (+S9) 0, 33, 100, 133*, 180*, 237* & 333* ug/ml (doses established by cytotoxicity screens; asterisks indicate the concentrations chosen for mutation frequency analysis). After exposure the cells were rinsed twice, resuspended for a 7-day expression period and replated at 10^5 cells/9-cm dish (10 replicates) in the presence of the selective agent 6-thioguanine (5 ug/ml) for 7-10 days before enumerating mutant colonies. 2 independent experiments were conducted using single cultures at each dose. Despite the success of the positive controls (-S9, 6 mM ethylmethanesulfonate; +S9, 8 mM dimethylnitrosamine) in increasing the # of mutant colonies per 10^5 cells (i.e., the number of cells capable of forming colonies in the presence of the selective agent), no such behavior is seen at any concentration of Dimethomorph regardless of the absence or presence of S9 microsomes. Dimethomorph is, therefore, not considered mutagenic under the conditions tested. **Acceptable.** (Rubin, 6/20/96)

CHROMOSOME EFFECTS

**** 52068-020 145439 843** "Evaluation of the Ability of Dimethomorph to Induce Chromosome Aberrations in Cultured Peripheral Human Lymphocytes" by E.J. van de Waart, RCC Notox B.V., Hambakenwetering, The Netherlands (project #058725; 8/23/91). Peripheral human lymphocytes in whole blood from a healthy male volunteer were cultured for 48 hr (0.4 ml blood in 5 ml medium) prior to exposure to test article (batch #KSLA/2; 98.6% dimethomorph), -/+ S9, for 2 hr followed by incubation for 21-23 hr or for 45-47 hr. Cell division was arrested during the last 3 hr by 0.5 mg/ml colchicine and chromosome spreads were produced for analysis. Doses, based on 2 cytotoxicity screens for inhibition of mitotic index (with the total # of cells with aberrations (-gaps) per 200 metaphases expressed in parentheses) were 0 (0), 10 (1), 100 (2) & 333 (2) ug/ml (24-h fixation) and 0 (6), 333 (2) & 422 (17) ug/ml (48-h fixation) in the absence of S9, and 0 (2), 1 (3), 10 (3), 333 (0) & 422 (48; $p<0.001$) ug/ml (24-h fixation) and 0 (1) & 422 (3) ug/ml (48-h fixation). Duplicate cultures were used. 100 metaphase spreads/culture were examined for aberrations. The results indicate that the number of aberrations increases at 422 mg/ml in both the absence and presence of S9. Most of the increase is associated with chromatid or chromosome breaks, or chromosome exchanges. The increase may be associated with high toxicity (expressed as an inhibition of mitotic index greater than 50% compared to controls) in those experiments in which a rise in chromosome aberrations is detected. The evidence suggests that dimethomorph is clastogenic in this system, at least in the presence of high toxicity. **Acceptable.** (Rubin, 6/19/96)

**** 020 145442 843** "Chromosome Aberrations in Cells of Chinese Hamster Cell Line V79" by H.G. Miltenburger, Laboratory for Mutagenicity Testing, Technische Hochschule Darmstadt, Germany (project #LMP 180 C; 8/14/86). CME 151-Z50 (Dimethomorph Technical; batch #Dw 11/86). Preparation of metaphase chromosome spreads was done 7 hr (high dose), 18 hr (low, mid & high dose) & 28 hr (high dose) after the beginning of the 4-hr test article treatment. Doses were (-S9) 0, 12, 60 & 160 ug/ml and (+S9) 0, 13, 60 & 170 ug/ml. For the 7-hr interval, colcemid was added 2 hr before harvest to cause metaphase arrest. For the 18 & 28-hr intervals, colcemid was added 2.5 hr before harvest. The cells were trypsinized, lysed, fixed and metaphase chromosome spreads prepared. 200 metaphases (100/duplicate culture) were analyzed at each dose. Positive controls were run only at the 18-hr interval. For the 7-hr, interval solvent control and treated percent aberrant cells excluding gaps was (-S9) 0.50 & 4.00 and (+S9) 0.50 & 3.50, respectively. For the 18-hr interval, these values were (-S9) 3.00, 2.50, 2.00 & 4.00, with the 0.94 mg/ml ethyl methane sulfonate positive control at 4.50, and (+S9) 0.00, 3.50, 1.00 & 1.00, with the 1.40 ug/ml cyclophosphamide positive control at 12.50. For the 28-hr interval, these values were (-S9) 0.50 & 1.50 and (+S9) 0.50 & 1.50. An apparent increase in % cells with aberrations thus occurred -/+ S9 at the 7-hr interval and -S9 at the 18 & 28-hr intervals. Chromosome breaks appeared to be the aberration most consistently induced. Note also that the system sensitivity is not high -S9 as evidenced by the apparently low percent of aberrant cells induced by ethyl methane sulfonate. CM-151 Z50 is a potential clastogen in V79 cells. **Acceptable.** (Rubin, 6/21/96)

**** 020 145443 843** "Chromosome Aberrations in Cells of Chinese Hamster Cell Line V79" by H.G. Miltenburger, Laboratory of Mutagenicity Testing, Technische Hochschule Darmstadt, Germany (project #LMP 275; 4/27/87). CME 151-Z50 (Dimethomorph Technical; batch #Dw 11/86). Preparation of metaphase chromosome spreads was done 7 hr (high dose; -/+ S9) and 18 hr (low, mid & high dose; -S9 only) after the beginning of the 4-hr test article treatment. Doses were (-S9) 0, 12, 60 & 160 ug/ml and (+S9) 0 & 170 ug/ml. Colcemid was added 2 (7-hr interval) or 2.5 (18-hr interval) before harvest to cause metaphase arrest. The cells were trypsinized, lysed, fixed and metaphase chromosome spreads prepared. 400 metaphases (100 per quadruplicate culture) were analyzed at each dose. Positive controls were run only at the 18-hr interval. For the 7-hr interval, solvent control and treated percent aberrant cells excluding gaps was (-S9) 1.25 & 3.50 and (+S9) 1.25 & 6.75, respectively. For the 18-hr interval, these values were (-S9) 1.25, 1.75, 1.25 & 3.50, with the 0.94 mg/ml ethyl methane sulfonate positive control at 6.50, and (+S9) with the 1.40 ug/ml cyclophosphamide positive control at 13.00. The increases in % cells with aberrations -S9 at the 7- & 18-hr intervals were statistically significant, but their biological significance is obscured because they were within the historical control range (0-4%). A larger effect was evident +S9 (7-hr interval). Chromosome breaks and, perhaps, isobreaks & fragments appear to be the

aberrations most consistently induced. While cytotoxicity is observed at the high doses (20-30% inhibition of mitotic index), it is not considered overwhelming. CM-151 Z50 is thus considered to be a clastogen in V79 cells. **Acceptable.** (Rubin, 6/24/96)

** 52068-021 145446 843 "Mouse Micronucleus Test on CME 151 Technical Material" by K.J. Proudlock et al, Huntingdon Research Centre Ltd., Huntingdon, England (project #SLL 169/89932; 10/17/89). CME 151 Technical Material (98.5% purity; batch #3 SRC Ref ST89/116). 15 mice/sex were exposed by intragastric gavage to 0 (aqueous 1% methylcellulose control, 20 ml/kg) or 5000 mg/kg test article (5/sex received 12 mg/kg mitomycin C as the positive control). 5/sex were sacrificed at 24, 48 & 72 hr post dose (positive controls at 24 hr only) and separate bone marrow smears prepared from each femur (though only 1 smear was ultimately analyzed). Smears were examined for micronucleated cells per 1000 polychromatic erythrocytes (PCE) per animal. PCE/NCE (normochromatic erythrocytes) was determined as an indicator of toxicity. There were no deaths. Clinical signs included piloerection and hunched posture, clearing by 4 hr post dose. Despite the success of the positive control in inducing a significant increase in micronucleated PCEs and a decrease in PCE/NCE, the test article had no discernable effect. **Acceptable.** (Rubin, 6/27/96)

** 52068-021 145447 843 "Micronucleus Test in Bone Marrow Cells of the Mouse with Dimethomorph" by E.J. van de Waart, RCC NOTOX B.V., Hambakenwetering, The Netherlands (project #058736; 7/31/91). Dimethomorph (98.6% purity; batch #KSLA/2). 15 mice/sex were exposed by intraperitoneal injection to 0 (DMSO control, 5 ml/kg), 20, 100 or 200 mg/kg test article (5/sex received 50 mg/kg cyclophosphamide as the positive control). 5/sex were sacrificed at 24, 48 & 72 hr post dose (low dose group at 48 hr only & positive controls at 24 hr only) and bone marrow smears were prepared from both femurs. Smears were examined for micronucleated cells per 1000 polychromatic erythrocytes (PCE) per animal. PCE/NCE (normochromatic erythrocytes) was determined per 1000 erythrocytes as an indicator of toxicity. 4 HD males and 7 HD females died w/i the 72 hr period. Clinical signs were not reported. Despite the success of the positive control in inducing a significant increase in micronucleated PCEs, such an effect was not seen with the test article. The positive control also caused a steep reduction in PCE/NCE ratio indicating marrow toxicity, in contrast to the low or non-existent decreases associated with the test article. Dimethomorph does not induce micronuclei under the conditions tested. **Acceptable.** (Rubin, 6/28/96)

SUMMARY
Increased frequency of chromosomal breaks were detected in three studies (see one-liners for record #s 145439, 145442 and 145443). These increases in structural chromosomal aberrations occurred either in the presence of excessive toxicity (>50% inhibition of mitotic index) or their biological significance was obscured because they were within historical control range (0 - 4%).

DNA DAMAGE

** 52068-020 145441 844 "Unscheduled DNA Synthesis in Hepatocytes of Male Rats In Vitro (UDS test)" by H.G. Miltenburger, Laboratory for Mutagenicity Testing, Technische Hochschule Darmstadt, Germany (project #LMP 180 A; 7/10/86). After a 1-hr pre-incubation of 3.5-4x10^6 primary hepatocytes/dose, CME-151 Z50 (batch #Dw 11/86; TGAI) and 1 mg/ml ^{3}H-thymidine were added for a further 3 hr @ 37^{o}C. Doses, based on a preliminary cytotoxicity screen, were 0, 2.5, 10, 25, 100 & 250 ug/ml. Each dose had 6 replicates. The flasks were placed in ice water to terminate the incubation followed by 2 rinses, cell lysis, nuclear lysis, DNA isolation and determination by scintillation counting of thymidine incorporation into DNA. Despite the success of the positive control (25.64 ug/ml dimethyl benzanthracene) in increasing by ~3-fold the incorporation of ^{3}H-thymidine into DNA (interpreted as an increase in repair DNA synthesis in quiescent cells), no such behavior was detected at any concentration of test article. CME-151 Z50 (Dimethomorph Technical) is, therefore not considered to induce repair synthesis under the conditions tested. **Acceptable.** (Rubin, 6/20/96)

** 52068-021 145445 844 "Cell Transformation Assay with Syrian Hamster Embryo (SHE) Cells" by H.G. Miltenburger, Laboratory for Mutagenicity Testing, Technische Hochschule Darmstadt, Germany (project #LMP 180 D; 9/3/86). CME 151-Z50 (Dimethomorph Technical; batch #Dw 11/86; 98.7% purity). All cells were secondary cultures. 500 target cells/dish were seeded onto 25-cm2 flasks that had

been seeded the day before with 40,000-60,000 irradiated feeder cells. After 24 hr test substance was added along with S9 microsomes (if appropriate). Test article was removed with a medium change at 6 hr (-/+ S9) or at 48 hr (-S9 only). Cultures were scored for transformed colonies (colonies showing criss-cross growth in the marginal zone and piling up in the middle) 7-9 days after the original seeding. 1000 colonies/dose from 10 parallel flasks/dose were scored. Doses and treatment times were established in an undocumented preliminary experiment. Doses were (6- & 48-hr treatment, -/+ S9) 0 (negative & solvent controls), 5, 10, 25 & 50 ug/ml, and (6-hr treatment) 0 (negative & solvent controls), 25, 250, 260 & 265 ug/ml. A dose-dependent decrease in colony forming efficiency (ranging between 100% and 47% relative survival) was noted under all conditions and indicated a cytoprotective effect of S9. Despite the ability of the positive controls to induce transformation (-S9, 0.5 ug/ml MNNG induced 1.7 and 1.6% transformation with the 6- & 48-hr treatments vs. 0% in controls; +S9, 5 mg/ml B[a]P induced 1.5% transformation with the 6-hr treatment vs. 0% in controls), at no test article concentration were more than 0.1% of the colonies transformed, and these were attributed to spontaneous transformation (the historical control rate of 0.06% is based on more than 60,000 colonies scored). CME 151-Z50 does not induce cell transformation under the conditions tested. **Acceptable.** (Rubin, 6/25/96)

NEUROTOXICITY

Study not submitted.

SUBCHRONIC STUDIES

90-Day Feeding Study

011; 145408; "Toxicity to Rats by Dietary Admixture for 13 Weeks with a 4-Week Withdrawal Period" (S.A. Ruckman et. al., Huntingdon Research Centre Ltd., Cambridgeshire, UK, Lab. Project # CMK 7/8624, 7/3/87). CME 151 (Batch # T2/85, Dimethomorph Technical) was administered orally in the diet to 10 Sprague Dawley rats/sex/dose at 0, 40, 200 and 1000 ppm (M = 0, 2.9, 14.2, 73.0 mg/kg/day, F = 0, 3.2, 15.8, and 82.0 mg/kg/day, respectively) for 13 weeks. An additional 10 rats/sex were added to the control and high dose groups and observed for 4 weeks to ascertain the reversibility of any treatment-related effects. All animals survived the study until scheduled sacrifice. No treatment-related clinical signs, body weight changes or food consumption were reported. Reduced lymphocyte counts in males and increased absolute liver and heart weights without any abnormal histological changes in females were detected at 1000 ppm. Except for the liver weights, all other changes were reversible. NOAEL (M/F) = 1000 ppm (73 and 82 mg/kg/day for males and females, respectively [**No adverse effects**]. NOEL (M/F) = 200 ppm (M = 14.2 mg/kg/day, F = 15.8 mg/kg/day, based on reduced lymphocyte counts and organ weight changes). **acceptable**. (Leung, 6/28/96).

4-Week Rat Feeding Studies

011; 145409; "4-Week Dietary Dose Range Finding Study in Rats" (K.Scott, et. al., Inveresk Research International, Musselburgh, Scotland, Lab. Project # 435025, 10/86). CME 151 (Batch # DW 11/86, 96.6% purity) administered orally in the diet to 10 Sprague-Dawley rats/sex/dose at 0, 2000, 3000, and 4000 ppm for 4 weeks (M: 0, 195.3, 285.8, and 372.5 mg/kg/day; F: 0, 215.0, 290.0, and 398.8 mg/kg/day, respectively). All animals survived the study until scheduled sacrifice. Clinical signs including piloerection, swollen abdomen, yellow staining perigenitally and thinness were reported in high dose animals. All treated females and high dose males exhibited reduced body weight gain (F: 68, 42, and 30% of control, respectively, $p < 0.05$; M: 64% of control, $p < 0.05$) with decreased food consumption in high dose males and females and mid dose females. Liver weights were increased in mid and high dose males and treated females. Liver hypertrophy were exhibited by mid and high dose males as well as treated females. NOEL (M) = 2000 ppm (195.3 mg/kg/day), (F) < 2000 ppm (215.0 mg/kg/day) based on liver weight changes and liver hypertrophy). **supplemental.** (Leung, 7/1/96).

011: 145410; "ZTH 236 Z 50 Preliminary Assessment of Toxicity to Rats by Dietary Admixture for 4 Weeks (Final Report)" (S. Warren et. al., Huntingdon Research Centre Ltd., Cambridgeshire, UK, Lab. Report # CMK 6/851056, 10/3/85). CME 151 (98.5% purity) administered in the diet to 5 Sprague-Dawley rats/sex/dose at 0, 200, 1000, and 5000 ppm for 4 weeks (M: 0, 15.8, 80.9, 305.9 mg/kg/day, respectively; F: 0, 17.5, 81.1, 283.2 mg/kg/day, respectively). One male and two females from the high dose group died. Body weight gain during the study was markedly reduced among male

and female rats receiving 5000 ppm ZTH 236 Z 50 (13.1% and 0.6% of control, $p < 0.01$). Clinical signs including loose feces, swollen abdomen, hunched posture, piloerection, emaciation, weight loss, brown nasal staining, lethargy and yellow/brown staining of the urogenital region were observed in animals from the high dose group. Reduced weight gain with food consumption were also reported in animals at 5000 ppm. Increased neutrophil count and platelets were noted in the blood of high dose males and females. Pathological exam revealed that the stomach of 3/4 males and 2/3 females at the high dose was distended with ingesta. Increased liver weights were reported in high dose males and females. NOEL (M/F) = 1000 ppm (M:80.9 mg/kg/day, F: 81.1 mg/kg/day, based on reduced body weight gain); **supplemental**; (Leung, 7/2/96).

13-Week Dog Feeding Study

012; 145411; "CME 151: 13 Week Dietary Toxicity Study in Dogs" (R.J. Greenough and R. Goburdhun, Inveresk Research International, Musselburgh, Scotland, Lab. project ID # 635212, 11/10/86). CME 151 (Batch # DW 11/86, 98.5% purity) administered in the diet to 4 beagle dogs/sex/dose at 0, 150, 450, and 1350 ppm for 13 weeks. All dogs survived the study until scheduled sacrifice. Clinical signs consisted of lip licking, occasional subdued behavior, and few instances of body tremors in high dose animals. Elevated alkaline phosphatase reported for high dose males during week 6 and 13 were not considered to be toxicologically significant in the absence of any histopathological changes. Increased absolute and relative thymus weights were noted in high dose males and reduced prostate weights were associated microscopically with an increase in fibrous tissue relative to glandular tissue. NOAEL (M/F) = 1350 ppm **[No adverse effects].** NOEL (M/F) = 450 ppm (based on clinical signs). **acceptable** (Leung, 7/2/96).

Supplemental Dog Feeding Study

012; 145412; "CME 151: Dietary Maximum tolerated Dose Study in Dogs" (R.J/ Greenough and R. Goburdhun, Inveresk Research International, Musselburgh, Scotland, Lab. Project ID # 635228, July, 1986). CME 151 (Batch # DW 11/86, 98.55 purity) administered in the diet to 1 beagle dog/sex in the following regimen: 1000 ppm for 7 days, 750 ppm for 7 days, 900 ppm for 7 days and 1200 ppm for 7 days. An additional pair of dogs (1M/1F) were dosed for 14 consecutive days at 1200 ppm. Clinical signs were confined to the male dogs and consisted of occasional incidences of emesis, subdued behavior and increased micturition. Males treated at 1200 ppm for 14 days exhibited slight body tremors. No adverse clinical signs were reported for females. Body weight losses with reduced food consumption were noted in male dogs treated with 1000 ppm (1.1 kg) or 900 ppm (0.3 kg). No treatment-related effects on hematology, biochemical or gross pathology were detected in dogs treated at 1200 ppm. **No adverse effects.** Maximum tolerated dose of CME 151 when administered to dogs in their diet is > 1200 ppm. **Supplemental**. (Leung, 7/3/96).

METABOLISM STUDIES

Rat Metabolism Studies

022; 145448, 145451; "The Biokinetics and Metabolism of 14C-Dimethomorph in the Rat" (H. Schluter, Shell Forschung GmbH, Schwabenheim, Germany, Lab. Project ID # SHGR.90.006, 8/24/90). Chlorophenyl-14C-dimethomorph (Batch # 2271-040, 98.5% radiochemical purity) and nonlabeled dimethomorph (Batch # H7879, 99.2% purity) were suspended in a 0.1% Tween 80 solution (S.A. varied from 0.23 - 2.45 mCi/g) and administered as single oral doses of 10 mg/kg (5M/5F), 500 mg/kg (10M/10F) or as multiple oral doses: pretreat 5 rats/sex daily with nonlabeled CME-151 for 14 days prior to pulsing with 10 mg/kg of 14C-CME-151 or received 10 mg/kg/day radiolabeled CME-151 for 7 days. No radioactivity was detected in expired air within a 24-hour period after dosing. Within 48 hours after dosing, 72.5% to 88.2% and 6.0% to 13.4% of the administrative radioactivity was excreted in the feces and urine, respectively. Urinary excretion in females receiving single or multiple oral doses of 10 mg/kg, was double that in males. However, following administration of 500 mg/kg, this sex-difference in urinary excretion pattern was not as distinct as after administration of the low dose. There was no evidence for accumulation in tissues and organs. The major pathways of metabolism consisted of demethylation of the dimethoxyphenyl ring and, to a lesser extent, oxidation of the morpholine ring. **acceptable.** (Leung, 7/15/96).

022; 145450; "14C-Dimethomorph (CME 151): Absorption, Distribution and Excretion after Bile Cannulation and Single Oral Administration to the Rat" (A. van Dijk, RCC Umweltchemie AG, Itingen, Switzerland, Lab. Project ID # 255172, 8/31/90). 14C-Dimethomorph (or CME 151, Batch S1050, 99% radiochemical purity) and nonlabeled CME 151 (Batch H7879, 99.2% purity) suspended in an aqueous solution of 0.1% Tween 80 and administered orally to 3-4 Sprague-Dawley rats/sex at 10.8 - 11.2 or 402 - 503 mg/kg after bile cannulation. By 24 hours after dosing, 95% and 35.8% of the administered radioactivity from the low and high dose, respectively, was eliminated in the bile. Urine and feces accounted for 6.4% and 5.8% of the dose at the low dose; whereas, urine and feces from the high dose rats contained 8.6% and 12.5% of the administered radioactivity, respectively. These results suggest that absorption of Dimethomorph is limited at the high dose level as compared to the low dose level. Glucuronidase-treatment of the bile collected from both sexes indicated that Dimethomorph is metabolized and mainly excreted via the bile after conjugation to glucuronides. The major aglycone was Z67 and/or Z69, representing 28.0% to 46.6% of the administered radioactivity for the low dose, and, 19.4% to 21.0% of the administered radioactivity for the high dose. **Supplemental**. (Leung, 7/16/96).